IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	No. 1:19-md-2875-RBK Hon. Robert Kugler
This relates to: All Actions	**Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion to Exclude Opinions of Laura Plunkett, PH.D.**

PLAINTIFFS' MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE OPINIONS OF LAURA PLUNKETT, PH.D.

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INTRODUCTION

Plaintiff's regulatory expert, Dr. Laura Plunkett is a pharmacologist, toxicologist, and United States Food and Drug Administration (FDA) regulatory specialist, who has been repeatedly admitted by courts as an expert for both plaintiffs and defendants. Dr. Plunkett has over thirty years of experience as a regulatory consultant. Between 1989 and 1997, Dr. Plunkett was employed as a manager of ENVIRON Corporation, where she worked in the areas of pharmacology, toxicology, human health risk assessment, and regulatory strategy. Since 1997, Dr. Plunkett has served as a private consultant to pharmaceutical companies in the process of developing and marketing FDA-regulated pharmaceutical products. Dr. Plunkett's consultations focus on issues related to pharmacology, toxicology, pharmacokinetics, human health risk assessment, and FDA regulatory compliance. Ignoring Dr. Plunkett's decades of experience, Defendants challenge Dr. Plunkett's qualifications to give both regulatory and science-based opinions. Defendants also urge the Court to exclude Dr. Plunkett's opinions regarding Defendants' valsartan based on objections that her opinions (1) impermissibly parrot Dr. Hecht and Dr. Bain; (2) are contrary to basic toxicology principles; (3) lack any discernible methodology; and (4) are improper legal opinions. Defendants also seek to exclude testimony that Dr. Plunkett provided at her deposition in response to questions from counsel, which they argue are undisclosed opinions. Defendants' objections are baseless, and their motion should be denied.

DR. PLUNKETT AND HER REPORT

Dr. Plunkett obtained a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. (Expert Report of Laura M. Plunkett, Ph.D., DABT, October 31, 2022 "Report", App'x A; ECF 2285-3). Dr. Plunkett's doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for

the cardiac toxicity of digitalis glycosides. (Report ¶ 3). After obtaining her Ph.D. in pharmacology, Dr. Plunkett was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland, with a focus on the autonomic nervous system and cardiovascular function. (Report ¶ 4). Dr. Plunkett was then an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where she performed research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. (Report ¶ 5). While at the University of Arkansas for Medical Sciences, Dr. Plunkett taught courses for both medical students and graduate students in pharmacology and toxicology, as well as neuroscience. (*Id.*). From 1989 to 1997, Dr. Plunkett was a manager of ENVIRON Corporation, where she worked specifically within the health sciences group, and most of her projects dealt with issues surrounding products or processes regulated by the FDA. (Report ¶ 6). Since leaving ENVIRON, Dr. Plunkett has formed her own regulatory consulting firms. (Report ¶ 1).

A common tool in all of Dr. Plunkett's work as a consultant is risk assessment. (Report ¶ 6). Dr. Plunkett has performed risk assessments for companies involved in initial product development and provided strategic advice to companies in early-stage development. (Report ¶ 7). Dr. Plunkett has knowledge and experience with FDA regulations that govern the manufacturing of drugs as well, *e.g.*, compliance with Good Manufacturing Practice (GMP) and US Pharmacopeia (USP) standards. (*Id.*). Dr. Plunkett has knowledge and expertise related to changes in the FDA regulations over the years from the initial passage of the Federal Food Drug and Cosmetic Act (FFDCA) in 1938 up to the most current amendments to the FFDCA (the Food and Drug Administration Reauthorization Act in 2017). (*Id.*). Dr. Plunkett's specialized regulatory knowledge resulted from courses she took that were offered through the Food Drug and Law

Institute (FDLI), experience while working at ENVIRON under the direction of former FDA employees, and experience gained while working as a consultant to industry since 1989. (*Id.*).

Dr. Plunkett is board-certified as a Diplomate of the American Board of Toxicology and is a registered patent agent in the US (USPTO Registration No. 45.015). (Report ¶ 2). From 2021 to 2022, Dr. Plunkett was the president of the Society of Toxicology Risk Assessment Specialty Section. (Report, App'x A). Dr. Plunkett has authored or co-authored numerous scientific publications, including a book chapter on pharmacovigilance practices in the United States and another on the regulation of food additives. (*Id.*).

Dr. Plunkett offers general opinions regarding the FDA's regulation of drugs and specific opinions regarding the Defendants' valsartan drug products. Dr. Plunkett's opinions are based on her knowledge and experience, an extensive review of regulatory documents, Defendants' own internal documents, and relevant literature. Dr. Plunkett utilized the same generally accepted methodology she applies in her ordinary course of professional work.

APPLICABLE LEGAL STANDARD

"Under the Federal Rules of Evidence, a trial judge acts as a 'gatekeeper' to ensure that 'any and all expert testimony or evidence is not only relevant, but also reliable.'" *Pineda v. Ford Motor Co.,* 520 F.3d 237, 243 (3d Cir. 2008) (citation omitted). Rule 702, the rule that governs expert testimony, has a "liberal policy of admissibility." *Id.* In essence, the expert testimony must meet the following requirements: "(1) the proffered witness must be an expert, i.e., must be qualified; (2) the expert must testify about matters requiring scientific, technical or specialized knowledge; and (3) the expert's testimony must assist the trier of fact." *Id.* at 244. Dr. Plunkett meets all elements required for the admissibility of her testimony.

A. Qualifications

The qualification requirement of Rule 702 is "liberally construed" and satisfied if an expert "possesses specialized expertise." *Geiss v. Target Corp.*, 2013 WL 4675377, at *4 (D.N.J. 2013) (citing *Pineda,* 520 F.3d at 244). **"**At a minimum, a proffered expert witness ... must possess skill or knowledge greater than the average layman...." *Aloe Coal Co. v. Clark Equip. Co.*, 816 F.2d 110, 114 (3d Cir.1987).[1] Dr. Plunkett clearly satisfies this standard.

B. Reliability

The second Rule 702 requirement (also known as reliability) is taken to "mean[] that the expert's opinion must be based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation.'" *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 742 (3d Cir. 1994) (citation omitted). While such "good grounds" for an expert's opinion are required, "[t]he grounds for the expert's opinion merely have to be good, they do not have to be perfect." *Id.* at 744. Good grounds may exist even if the court believes there "are better grounds for some alternative conclusion" or that "a scientist's methodology has some flaws such that if they had been corrected, the scientist would have reached a different result." *Id.*

Moreover, proponents of expert testimony do not have to "demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are *correct*, they only have to demonstrate by a preponderance of evidence that their opinions are reliable." *In re DVI, Inc. Sec. Litig.*, 2014 WL 4634301, at *5 (E.D. Pa. Sep. 16, 2014) (internal quotation marks omitted) (emphasis original); *see also In re Paoli*, 35 F.3d at 744 ("[the] evidentiary requirement of

[1] *See Waldorf v. Shuta,* 142 F.3d 601, 627 (3d Cir. 1998) wherein the Third Circuit adopted a broad view regarding expert qualifications in finding that a social worker with qualifications that are "a little thin" could serve as a vocational expert, since he had substantially more knowledge than an average layperson regarding employment opportunities for disabled individuals.

reliability is lower than the merits standard of correctness"). Scientific study is not the only basis for an expert's reliability, which may also be founded upon experience. As the Supreme Court later added in *Kumho Tire*, the objective of *Daubert* "is to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). Indeed, the *Daubert* test "may be more flexibly applied in cases where the expert testimony is based on experience." *In re Front Loading Washing Mach. Class Action Litig.*, 2013 WL 3466821, at *2 (D.N.J. July 10, 2013). Moreover, in the case of experience-based opinions, the fact that an expert has been determined to be qualified weighs in favor of the reliability of her report. *Altieri v. State Farm Fire & Cas. Co.*, 2011 WL 1883054, at *3 (E.D. Pa. May 17, 2011).

C. Relevance

The third requirement of Rule 702, known as relevance, is satisfied "if an opinion fits a particular case (and thus helps the trier of fact)" – i.e., there must be a "connection between the scientific research or test result to be presented and particular disputed factual issues in the case." *Geiss*, 2013 WL 4675377, at *5 (internal quotation marks omitted).

ARGUMENT

A. Dr. Plunkett's "Science-Based Opinions" And "Chemistry-Based Opinions" Should Be Allowed

Defendants seek to exclude what they deem Dr. Plunkett's "science-based opinions," such as Dr. Plunkett's opinion that the valsartan drug products containing the highly potent genotoxins NDMA and NDEA rendered them unsafe, even at nanogram levels. (Def. Br. at 5, ECF 2285-1). These opinions interface with Dr. Plunkett's regulatory opinions, namely that such unusually potent impurities must be controlled at a level even lower than below 0.1 percent. (Report ¶ 30).

Defendants similarly seek to exclude Dr. Plunkett's "chemistry-based opinions," such as what was knowable related to nitrosamine formation at the time Defendants should have performed an initial risk assessment. (Def. Br. at 7). Dr. Plunkett is qualified to offer these opinions and had a reliable basis for these opinions.

1. Dr. Plunkett Is Qualified to Provide "Science-Based Opinions"

Under Rule 702, an expert must be qualified "by knowledge, skill, experience, training, or education. Fed. R. Evid. 702. The standard for expert qualification is a liberal one. *Pineda v. Ford Motor Co.,* 520 F.3d 237, 243 (3d Cir. 2008). Defendants claim that Dr. Plunkett is not qualified to provide opinions related to the human health risk associated with the presence of nitrosamines in valsartan. (Def. Br. at 6). In making this argument, Defendants apparently conflate "risk assessment" with "causation," and "medical opinions" lumping both types of opinions under the heading "science-based opinions," though Dr. Plunkett offers only the former. (Def. Br. At 6–7.) However, Defendant's own misunderstanding of Dr. Plunkett's specialties of toxicology and pharmacology does not render her unqualified. Indeed, as numerous courts have held, Dr. Plunkett is highly qualified with respect to both toxicology and pharmacology—the disciplines that serve as the basis for her discussion of valsartan's safety profile in the regulatory context.

Dr. Plunkett has over thirty years of experience in the areas of pharmacology and toxicology and has worked in both government and academic research. Dr. Plunkett's graduate training was in cardiovascular pharmacology and valsartan is a cardiovascular drug. Dr. Plunkett has worked extensively for decades on projects related to the regulation of human drugs by the FDA—core disciplines of FDA regulation of human drugs are pharmacology (efficacy) and toxicology (safety). (Report ¶ 7). Dr. Plunkett has taught pharmacology and toxicology at the undergraduate and postgraduate levels, and currently holds an adjunct appointment in the

Department of Environmental Science, Baylor University. As an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Dr. Plunkett's work was directed toward understanding the biological mechanisms of drug actions, including both the therapeutic effect and the toxic effects of drugs. (Report ¶ 5). Courts agree that Dr. Plunkett is qualified to testify in the area of risk assessment. *See, e.g., Broussard v. Multi-Chem Grp., LLC*, 255 So.3d 661, 680 (La. Ct. App. 2018) ("Dr. Plunkett has qualified in the past as an expert to assist the courts in determining what chemicals were in fires, assessing whether there exists sufficient information to make health assessments, and determining what types of exposure one would expect to find. She has also testified on behalf of defense law firms in these types of cases" and "trial court accepted Dr. Plunkett's testimony regarding the risk posed by the fire's emissions."); *In re Taxotere Docetaxel Prods. Liab. Litig*. 2021 WL 3124494, *3 (E.D. La. July 23, 2021) ("The Court finds that Dr. Plunkett has performed the appropriate analysis to offer this opinion. This opinion does not speak to causation but rather to association and whether there was a basis to believe a causal relationship existed."); *Terry v. McNeil-PPC, Inc (In re Tylenol (Acetaminophen Mktg., Sales Practices, & Prods. Liab. Litig.)*, 2016 WL 4039329 (E.D.Pa. July 28, 2016), *6 ("I see nothing improper about her methodology. Dr. Plunkett may offer opinions related to general causation on the issue of dose."); *In re Gadolinium-Based contrast Agents Prods. Liab. Litig*., 2010 WL 1796334, *14 (N.D. Ohio May 4, 2010) ("The Court finds that Dr. Plunkett's background in pharmacology with expertise in pharmacokinetics, toxicology, risk assessment generally and her prior work on GBCA risk assessment specifically, more than adequately qualifies her to opine on NSF causation, the stability of Omniscan, and the free gadolinium theory."). Dr. Plunkett is adequately qualified to provide "science-based opinions."

2. Dr. Plunkett Had a Reliable Basis for Her "Science-Based Opinions"

Dr. Plunkett provides several regulatory opinions that also touch on the risk posed by the nitrosamines in valsartan. Dr. Plunkett explains that in order for a generic drug to be therapeutically equivalent, it must also be pharmaceutically equivalent—meaning it must have the same clinical effect and safety profile —and that valsartan with nitrosamines does not have the same safety profile as valsartan without nitrosamines. (Report ¶ 21). Similarly, Dr. Plunkett opines that impurities that are unusually potent in producing toxic effects should be controlled at a level even lower than below 0.1 percent. (Report ¶ 30).

In giving the opinion that nitrosamines are unusually potent and their presence alters the safety profile of valsartan, Dr. Plunkett in part relied on ICH guidances including ICH M7(R1), which lists NDMA and NDEA as known human carcinogens and genotoxic compounds. (Report ¶ 33). Dr. Plunkett also relied on the National Toxicology Program (part of the Department of Health and Human Services within the US government), which classified both NDMA and NDEA as carcinogens in 1981 as part of the Report of Carcinogens, a science-based public health document prepared for the HHS Secretary on a routine basis. (Report ¶ 42). Dr. Plunkett then cited statements from the International Agency for Research on Cancer (IARC) in 1972 on NDMA and NDEA being potent carcinogens. (Report ¶ 43). Dr. Plunkett also quoted a 1991 textbook on the toxicology of NDMA and NDEA:

> N-nitroso Compounds. This major class of important chemical carcinogens is characterized by chemicals derived from secondary amines or amides by nitrosation. Nitrosamines and nitrosamides are synthetic as well as natural occurring substances. They were discovered to be carcinogenic only in the last 35 years beginning with the findings of Barnes and Magee of England that dimethylnitrosamine, an industrial solvent that caused jaundice and liver damage in workmen exposed to it, was highly hepatotoxic in rodents where it reproduced lesion seen in humans, subsequently they demonstrated that this chemical was among the most carcinogenic chemicals then known. Some of the first studies on alteration of DNA

> by carcinogens were performed with nitrosamines and their patterns of alkylation of DNA have now been extensively documents.

(Report ¶ 40). Dr. Plunkett also cited Defendants' internal documents where they recognized that n-nitroso-compounds are high potency genotoxins. (Report ¶ 54). These are exactly the kinds of documents Dr. Plunkett has relied on in evaluating the safety profile of pharmaceutical products while working as a toxicology, pharmacology, and regulatory specialist in the field. Dr. Plunkett had a reliable basis in concluding, "the carcinogenicity of NDMA has been understood for many decades and there is no controversy surrounding the fact that the compound is highly potent as a carcinogen." (Report ¶ 40).

3. Dr. Plunkett's Opinion That There Was No Acceptable Specification for Nitrosamines in Valsartan Is Not An "Any Exposure" Opinion

Defendants couch Dr. Plunkett's opinion that prior to the recall there was no allowable amount of nitrosamines in valsartan as an "any exposure" opinion. (Def. Br. at 14). Dr. Plunkett is not providing an "any exposure" general causation opinion. Instead, Dr. Plunkett provides an opinion as to the specification for nitrosamines set by regulatory bodies and used in risk assessments to assess the safety profile of the drug. Dr. Plunkett does not determine whether valsartan causes cancer and does not, herself, determine what the acceptable specification should be. Rather, she cites the Defendants' own internal documents that note in 2019 the FDA determined that there is no acceptable specification for nitrosamines in valsartan. (Report ¶ 49). Dr. Plunkett testified as follows when asked what dose is necessary to increase the risk of cancer:

> Q. You did say you're testifying that the presence of impurities in Valsartan increases the risk of cancer. And I'm asking what is the minimal doses at which that happens?
>
> A. And again, I'm answering it to you, I already have, in the literature – this is where I need to explain. I'm not trying to be nonresponsive, but let me just step back a second and state that if you remember, you understand as I said that I believe that NDMA and NDEA have been identified by authoritative bodies as carcinogens, probable human carcinogens, based on the data that's there. If you – with that in

> mind, and looking at what this drug, what the FDA has said and what other, how you would approach risk assessment for these kinds of products in the context of pharmaceutical risk assessments or risks are looked at in the context of benefits, in this case you're talking about how does the risk of cancer balance against what is going on with the drug. And as a result of that work, I'm saying to you that it's very clear as a toxicologist, pharmacologist, risk assessor, someone who works in regulatory affairs, that the presence of this ingredient in Valsartan, where there is no known safe dose generally of these impurities, that it applies to any particular individual, because you have to do this on an individual basis based upon their exposure assessment; but generally the statement is that it increases the risk of cancer. It increases the risk in that particular person that you may want to consider that they would have an outcome of cancer. And then from that, the role of the specific causation expert or the risk assessors in the litigation would be to talk about the specific level of exposure. So that's why I'm saying that's beyond what I did. I looked at this from the aspect of the regulatory expert, as a toxicologist, what do I know, and I know that these were probable human carcinogens. They are not supposed to be in the Valsartan, or the presence of them as very potent genotoxins increases the risk of cancer.

(Plunkett Depo 15:7-16:22, ECF 2285-4). Defendants continued to try to contort Dr. Plunkett's risk assessment opinions into an any exposure opinion:

> Q. I've always heard the expression that when it comes to toxicology, one of the major tenets is that the dose is in the poison, or the poison is in the dose. Is that a true – an expression that's used in toxicology?
>
> A. It is a term that's used. But there's a different – there's a different sort of methodology or way for assessing risk and dose issues with cancer versus non-cancer. So that's absolutely the issue of threshold mechanism or a threshold existing for things that are doing, actively to produce effects that are not cancer. You can typically find a threshold if you do enough studies or do enough looking. However, for cancer risk assessment, if the assumption is that there is no threshold, so as a result, the dose makes the poison can apply, but it's not to the same extent or level as it does when you're talking non-cancer endpoints.
>
> Q. When you describe something as a potent genotoxic, in order to determine when it's a potent genotoxin do you need to know what dose the person is exposed to?
>
> A. I'm not talking about as a person, I'm talking about based upon scientific evidence. And by "potent genotoxin," I'm describing the fact that the studies that have been done, genotoxicity studies are typically done in vitro. There are some in vivo studies but most of it's done in vitro. And in those studies, when you compare, again when you look at cross-compounds, NDMA is often a positive control compound. It's used to make sure your assay is working properly. So in other words, it is reliably going to produce a genotoxic insult when you expose cells to it, and

> the potency has to do with the fact that you can get those kinds of DNA changes or changing mutations at very low exposure levels.

(Plunkett Depo 33:21-35:9). Dr. Plunkett does not provide an any exposure opinion and her opinion that no nitrosamines were allowed in valsartan prior to the recalls is based on FDA statements and is admissible.

4. Dr. Plunkett's "Chemistry-Related" Regulatory Opinions Are Permissible

Defendants claim that Dr. Plunkett merely parroted the chemistry opinions offered by Dr. Hecht. (Def. Br. at 8).

Experts may cite to, incorporate, or even rely on the opinions and materials of other experts of a litigation. *E. Allen Reeves, Inc. v. Michael Graves & Assoc., Inc.*, 2015 WL 105825, *5 (D.N.J. 2015) ("An expert, however, may rely on the opinion of another expert in formulating his or her opinion"); *see also Callas v. Callas*, 2020 WL 3468084, *8 (D.N.J. June 25, 2020) (rejecting argument that one plaintiff's expert "parroted" another where they "relie[d] upon and incorporate[d] into his report" the first expert's conclusion). This is exactly what Dr. Plunkett did here. Dr. Plunkett linked some of the opinions of Dr. Hecht to the applicable regulatory standards. For instance, in the context of the FDA statement, "when feasible, manufacturers of API and drug products should take reasonable steps to prevent or eliminate N-nitrosamines," Dr. Plunkett noted that Dr. Hecht opined that it *was* feasible to prevent the formation of NDMA and NDEA in valsartan because chemical processes existed to make valsartan that do not produce NDMA or NDEA impurities. Therefore, if the jury were to believe Dr. Hecht (who relied in part on ZHP's own deviation investigation report in part) that it was feasible to prevent the formation of NDMA and NDEA in valsartan, then the N-nitrosamines in valsartan should have been prevented or eliminated per the FDA. (Report ¶ 49). Similarly, Dr. Plunkett explains that it is the manufacturer's responsibility to ensure the quality of its valsartan as part of its cGMP regulatory obligations, then

notes that the introduction of NDMA and NDEA into valsartan was foreseeable as established by Dr. Hecht's expert report and the testimony of ZHP's deputy director of technical affairs, Dr. Peng Dong'. (Report ¶ 46).

Dr. Plunkett also has independent knowledge and basis for her "chemistry related" opinions, including specifically related to the chemical structure of NDMA and NDEA. For example, Defendants elicited the following testimony during Dr. Plunkett's deposition:

> Q. Prior to being contacted about serving as an expert in this case, did you personally have knowledge about how any chemical process could lead to the formation of NDEA?
>
> A. NDEA? Um -- yes. I mean, I have reviewed the toxicology literature over the years related to these types of impurities and actually, in the EPA projects I've worked on, on the carbon contaminants in that particular case, which is a little different than the FDA world. But yes, I have reviewed the formation. I have some -- in fact, the structures that I put into my report come from one of my textbooks, and I've reviewed that section and that chapter of the textbooks several times in the past, so I have that awareness. But I've never worked -- I had not, you know, I have not developed a report before for anyone, none of my clients ever approached me to put together a tox profile on NDEA specifically. So it's more general of understanding and training based upon the toxicology training I've had.

(Plunkett Depo 25:24-26:21). Additionally, Dr. Plunkett's "chemistry-related opinions" interface with her regulatory opinions, including whether the company fully complied with regulatory standards or conducted an adequate risk assessment. Dr. Plunkett provided the following testimony on the topic:

> Q: You do provide an opinion that it was known in 2012 that DMF could degrade into diethylamine, right?
>
> A: Yes, based on that – I think if you read my report I talked about the fact that when a company is doing a risk assessment, part of that would be search of the published literature to make sure that there is something that is out there that they may not be aware of. So certainly, that's why I have formed those opinions. If I was to do a risk assessment for looking at something about the process that's being used, I could look at what the potential byproducts or degradation products or pathways that could be affected by using this particular chemical process. And so that's why those articles are important, because it shows what was known at different points in time and, most importantly, what was known before the issues

> arose in this case about the breakdown of – or the use of the chemical process that led to the presence of the NDMA and NDEA in the Valsartan API.
>
> Q: The only published literature you cite on those topics is published literature that was used by Plaintiffs counsel in depositions, correct?
>
> A: Yes. And again, that's because that was beyond the scope of what I was asked to do. I was not asked to be the chemist to address that specific question in a complete and expansive manner.
>
> Q: So your opinion of this was widely known, is based on documents that you obtained through this litigation, correct?
>
> A: Well, depends. I also have – I also – well, not entirely – are you asking me specifically just about the issue of breakdown or the formation of DMF for example, that's what you're asking me?
>
> Q: Correct.
>
> A: That would be true that – because again, that was beyond the scope of what I did independently, but it's evidence that's important to me in my opinions because one of the issues that you have as a regulatory expert is understanding what a company could or should have done if they had been following all the regulations and been complying fully with what they are required to do in the literature to produce a human prescription drug.
>
> Q. I understand, but my question is really simple. Your opinions of what the company could and should have known are based on documents you obtained in this litigation, correct?
>
> A. That and their own deposition testimony. So the company – ZHP company witnesses also agreed to that issue, that these are things that could have been known. They had not done a rigorous assessment.
>
> Q. What ZHP witness said that they did not do a complete risk assessment?
>
> A. So there's a stipulation document that's in the paragraph, paragraph 45 in my report, where I say that the lack of full evaluation of chemical processes have been stipulated to be Defendants. So evaluation – full evaluation is what I'm talking about in terms of the risk assessment.

(Plunkett Depo 29:18-32:6). Dr. Plunkett has an independent basis for her opinions and does not merely parrot Dr. Hecht as the Defendants suggest. In addition to providing limited citations to Dr. Hecht's opinions in order to link them to applicable regulatory standards, Dr. Plunkett provided

her own opinions derived from her own experience and analysis. Dr. Plunkett's "chemistry-related opinion" should be permitted.

B. Dr. Plunkett's Regulatory Opinions Are Permissible

1. Dr. Plunkett is Qualified to Provide Regulatory Opinions

Defendants argue as an initial matter that Dr. Plunkett should be precluded from offering regulatory opinions because she does not have any regulatory training. (Def. Br. at 16). Dr. Plunkett has extensive regulatory training and experience through her decades of work as a regulatory consulting specialist to industry, as discussed *supra*. Defendants elicited the following testimony on Dr. Plunkett's regulatory experience during her deposition:

> Q. I'd like to know the names of all medications for which you have provided consulting services to pharmaceutical companies.
>
> A. So most of the work that I do, have done over the years with companies is considered confidential. I don't even share names. Companies typically that I'm currently working for, because that's part of my business terms and part of the agreements that I'm asked to enter into by companies. I have testified before that in my, over my 30-plus years experience, I have worked on projects related to many of the largest drug companies around, and many small companies as well. But I don't feel that it's something I could do to divulge the specifics of a project without asking a company to do that, if I could do that or not. I assume you're limiting that to regulatory consulting. You're not asking about the litigation work, because that you could find, when you – if you look at my trial work.
>
> Q. Have you ever done any litigation work on behalf of a pharmaceutical manufacturer?
>
> A. Yes. I did litigation work on behalf of pharmaceutical manufacturers when I was working with Environ between 1989 and 1997. They only worked for industry in litigation. And there is a most recent time would have been, probably about ten years ago, I worked for a company, a Japanese company on an issue that was being litigated. A Japanese drug company.
>
> Q. What was the drug?
>
> A. Oh, gosh, I don't remember the name off the top of my head. A blood pressure medicine, but I don't remember the name off the top of my head.

(Plunkett Depo 39:9-40:19).

Ignoring Dr. Plunkett's extensive regulatory experience, Defendants instead argue that Dr. Plunkett is not experienced enough to provide regulatory opinions because she has never worked at the FDA, consulted for the FDA, or been invited to speak to the FDA regarding her views on nitrosamines. (Def. Br. at 17). Defendants' contrived standards are not requirements to provide regulatory expert opinions, as evidenced by courts routinely admitting Dr. Plunkett's regulatory expert opinions. *See*, *e.g.*, *Tsao v Ferring Pharms*, 2018 WL 148265, *10 (S.D. Tex. Mar 26, 2018) ("Dr. Plunkett is qualified to give expert testimony regarding FDA regulations (including new drug approval and recalls)"); *Terry v. McNeil-PPC, Inc (In re Tylenol (Acetaminophen Mktg., Sales Practices, & Prods. Liab. Litig.)*, 2016 WK 4039329, *8 (E.D. Pa. July 28, 2016)("Dr. Plunkett's testimony about the Tylenol label are made in reference to her opinions as a regulatory expert—about what actions she believes the defendants should have taken to fulfill their legal duties as a drug manufacturer. She is qualified to offer such an opinion."); *In re Xarelto Rivaroxaban Prods. Liab. Litig*., 2017 WL 1352860, *2 (E.D. La. April 13, 2017) ("She is neither a medical doctor nor a regulatory agent for the FDA but has extensive experience consulting and advising as to regulatory matters, including label content. The Defendants do not dispute Dr. Plunkett's qualifications, and this Court finds she is well-qualified by her experience and education. The Court further finds that Dr. Plunkett's opinions are based on her review of Defendants' and the FDA's statements and documents, as well as medical journals and reports.").

Dr. Plunkett is a well-qualified regulatory expert and her opinions in this litigation are based on her review of Defendants' and the FDA's statements and documents, as well as medical journals and reports. As such, Dr. Plunkett is qualified to provide regulatory opinions in this litigation.

2. Dr. Plunkett's Regulatory Opinions Do Not Usurp the Role of the Court or Jury

Defendants argue that Dr. Plunkett's opinion that valsartan with NDMA or NDEA present was deemed adulterated per FDA standards is impermissible because it would usurp the role of the Court and the jury. (Def. Br. at 20). However, that is not just Dr. Plunkett's opinion: the FDA *actually* deemed valsartan API with NDMA or NDEA present adulterated and valsartan finished dose with NDMA or NDEA present was recalled for that reason. (Plunkett ¶ 59 (citing FDA's Warning Letter to ZHP)). It is well within the parameters of *Daubert* for an expert to detail the legal and regulatory frameworks and decisions that affect industry. *Sec. & Exch. Comm'n v. McDermtt*, 2022 WL 9252895, *13 (E.D. Pa. Mar. 30, 2022) ("Even though [the expert] goes into detail on the regulatory framework … she does not usurp the court's role of explaining the law to the jury… As an expert in industry custom and practice, [she] can testify to the ways in which industry custom and practice are shaped by legal frameworks.") (quotations omitted). Dr. Plunkett's explanation of regulatory frameworks and decisions and, in particular, the FDA's actions in deeming the drug to be adulterated falls squarely within these parameters.

It is Dr. Plunkett's opinion that the FDA deeming valsartan API with NDMA or NDEA present as adulterated applied not only to the valsartan API with NDMA or NDEA present at the exact moment the FDA made its adulteration determination, but also valsartan API with NDMA or NDEA present prior to the day the FDA released its adulteration determination and finished dose product that used valsartan API with NDMA or NDEA. (Plunkett ¶ 62). Dr. Plunkett testified as follows on the subject of adulteration:

> Q. When did you first form the opinion that Valsartan that contained NDMA and/or NDEA impurities was adulterated?
>
> A. The opinions I've expressed in my report, where I talk about the products that would be deemed adulterated, would have been developed at the time I wrote the report so then before the date of the report, October 31st, would have been sometime

> earlier in 2022. I can't give you an exact date. And I would state that the – and those opinions were developed based on a review of findings of FDA along those lines, where they actually sent a warning letter related to that.
>
> Q. When did the FDA send a warning letter – when did the FDA first send a warning letter related to that.
>
> A. I want to say that there's a warning letter that I'm aware of in 2019. I don't know if there were other warning letters that existed. I don't know and the one I'm thinking about is one that went to ZHP.
>
> Q. Do you hold the opinion that Valsartan was adulterated before that – before 2019?
>
> A. It's my opinion that it would have been deemed adulterated based on what was – what the evidence in the case appears to show, yes.
>
> Q. What –
>
> A. Based on –
>
> Q – I didn't mean to interrupt you. So Sorry.
>
> A. No, go ahead and follow up, because I think you were going to ask it for me, right? If that's what I mean by that. I mean that – if the facts and evidence in this case show that at least at the time that Novartis identified – I described this in my report in 2018 to ZHP – the presence where they had found it, the presence when it's found indicates that it's adulterated because it is not something that was meant to be there, and it is a potent genotoxin, and that's been known from well before that time period. In this particular case, there's also facts and evidence to indicate that as early as the 2014 time frame, the company, being ZHP, was making product where there were unidentified peaks that they were not pursuing. So the presence of those impurities, the fact that for a time raises questions about the quality of the product, even though they had not identified those particular ones at that particular time as being, for example, NDMA.

(Plunkett Depo 43:15-44:18). Dr. Plunkett came to the same adulteration conclusion when applying her same methodology to a hypothetical posed to her during her deposition on name brand valsartan:

> Q. If Diovan, if some of the Diovan manufactured by Novartis had trace amounts of NDMA or NDEA, would that change your opinion that ZHP's Valsartan is adulterated?
>
> A. I don't think it would change my opinion that I would deem them adulterated because the presence of those particular compounds, as the FDA concluded, was

> that they were adulterated. And the fact that they were being produced outside of good GMP on top of the presence of those impurities would, by the definitions, the regulatory definitions, deem them adulterated. That's in my report as well.

(Plunkett Depo 123:4-24). Dr. Plunkett's adulteration opinions are reliable and consistent with determinations made by the FDA.

3. Dr. Plunkett's Opinion Does Not Parrot Dr. Bain

Defendants argue that Dr. Plunkett merely parroted the opinions of Dr. Bain. (Def. Br. at 19). Dr. Bain's name does not appear anywhere in Dr. Plunkett's expert report or reliance list, because Dr. Plunkett had not reviewed Dr. Bain's expert report prior to finalizing her own expert report on October 31, 2022. Dr. Plunkett elaborated on the delineation between herself and Dr. Bain during her deposition:

> Q. Are you offering an opinion that ZHP's QMS was inadequate?
>
> A. You already asked me that, and I said that was beyond the scope. That's something that Dr. Bain, I believe, is addressing.
>
> Q. So if that's the case, if it's beyond the scope, why do you mention QMS in your report?
>
> A. To give context to why, what companies are required to do, because I talk about responsibilities, overall responsibilities of what a drug manufacturer is supposed to do, and I also talk about limitations of the FDA. And those are both important context opinions or – not opinions, context to give when I talk about different issues in the case. And I was asked in this case to provide a general overview of some of the important regulatory issues that the company would need to address, things they have to have in place, or things they should be doing in order to be manufacturing the drugs in compliance with, generally with FDA regulation.
>
> Q. Other than the fact that you have testified already today that ZHP did not conduct, in your opinion, an adequate risk assessment, do you have any other opinions as to things that you believe ZHP did that were contrary to FDA regulation.
>
> A. Well, several times in my report I say that they put patient health at risk because of the actions they took. They are not doing – not doing the risk assessment, for example, to understand that they were selling a product, or marketing a product that had these toxic contaminants – toxic impurities, carcinogens in them. I'll look, I mean, I have a couple of – I have a summary – I have a summary opinion.

> Q. No, no.
>
> A. – at page –
>
> Q. I don't think you're understanding my question. Other than the risk assessment requirement, are there any specific FDA regulations that you are saying ZHP did not comply with?
>
> A. I don't think I state my opinion the way you're stating it. But I certainly do think some of my opinions are relevant to the question you're asking. I don't know how else to answer it. So you'll notice in my report, I think you'll notice in my report that you don't see a number of statements that say "They violated this regulation," or, "They violated that regulation." Because that analysis was being done by, in my – the information was given in the reports I've seen by other experts. Instead, what I have provided, I believe, in my report, is, I have talked about what are the responsibilities of a manufacturer under regulations, what regulations apply to them, and what issues I see. And I see issues with the improper risk assessment, for example, which leads to them producing a product that I believe would be deemed adulterated. So I guess what I'm saying, it's being deemed adulterated, that's a violation of the – of the regulations that deal with adulteration of products under the – under both the law itself, section 351 CFR; and also other parts of the – the quality regulations that talks about the need to produce a product that is – that is not adulterated.

(Plunkett Depo 145:3-147:19). Dr. Plunkett does not parrot or even rely on Dr. Bain in providing her regulatory opinions. To the extent there is overlap that is obviously permissible. Defendants' argument that Dr. Plunkett merely parrots Dr. Bain is without merit.

C. Dr. Plunkett's Regulatory Opinions Regarding the Finished Dose Manufactures Should Be Permitted

Defendants criticize Dr. Plunkett for reviewing less documents with a finished dose manufacturers' bates stamp than documents with a ZHP bates stamp. (Def. Br. at 23). Dr. Plunkett reviewed ample documents from the finished dose manufacturers to provide her opinions, including those produced by the finished dose manufacturers and the many ZHP documents and evidence produced which directly apply to the finished dose manufacturers. Providing a regulatory opinion such as the following does not require reviewing a voluminous number of company documents: "While ZHP did not comply with its quality agreements, it is still the finished dose

manufacturer's responsibility to ensure that the API they are purchasing and the finished dose they are selling do not contain harmful impurities. Quality agreements do not absolve finished dose manufacturers from their responsibilities regarding drug quality." (Plunkett ¶ 55). Dr. Plunkett also opined, "At any point in time, ZHP could have, without FDA authorization, changed their process as they indicate later in 2019 (i.e., quenched outside the presence of the drug product) and ANDA holders could have sold valsartan finished dose utilizing valsartan API quenched outside the presence of the drug product, resulting in the sale of valsartan finished dose without the presence of NDMA or NDEA impurities." (Plunkett ¶ 28). Again, this regulatory opinion related to the finished dose manufacturers does not require reviewing thousands of internal company documents. This is at most an issue for cross-examination, as with most of the other issues raised.

D. Dr. Plunkett Does Not Offer Undisclosed Opinions

Defendants wrongly assert that Dr. Plunkett opined that the finished dose defendants were required to obtain access to the closed portion of the valsartan Drug Master File. (Def. Br. at 25). However, Defendants miss an important distinction. Dr. Plunkett testified that the finished dose manufacturers *should* have obtained access to the closed portion of the Drug Master File, not that they were required to:

> Q. Do you believe that Teva should have obtained access to ZHP's Drug Master File?
>
> A. Yes, I do.
>
> Q. Do you believe that Torrent should have obtained access to ZHP's Drug Master File?
>
> A. Yes, I do.
>
> Q. Why should the finished dose manufacturers have obtained access to ZHP's Drug Master File?

> A. It's the – the only way that they would be able to assure themselves that the API company, in this case, ZHP, had done a complete and proper risk assessment, especially given that the processes had changed from the TIN process that was part of the Diovan RLD monograph.

(Plunkett Depo 323:3-17). Defendants also argue that Dr. Plunkett's opinion that the finished dose manufacturers should have obtained access to the closed portion of the Drug Master File must be excluded because it is not contained in her expert report and was not offered until the end of her deposition. (Def. Br. at 25). Contrary to Defendants' suggestions, that testimony is part of the overall context of her opinions and clearly contemplated in the report, and Dr. Plunkett's deposition testimony demonstrates that she initially offered such testimony in response to questions from Defense counsel which injected the issue:

> Q. And you're familiar with the closed portion of the DMF that is not available and visible to the finished dose manufacturer in the course of getting an ANDA approved, etc., right?
>
> A. I am aware that Drug Master Files are typically closed unless companies come to an agreement to share information. That's why I mentioned getting – I don't know what you call it, a confidentiality agreement, a nondisclosure agreement of information, and that's why I asked, did those exist, and I was told that there was no indication that they did in the discovery documents.
>
> Q. Is your criticism of Teva that they failed to seek access to the closed portion of ZHP's DMF?
>
> A. Yes, given that – give the situation that existed here, that's exactly right. I mean, again, this is advice I've given to clients before, when they are talking about having responsibility for something else, that another company does that, it's not within their purview. In fact, if you look at – I know you have limited time, sorry, but in a – I cite to a document in my reliance materials that is a presentation put on by the FDA about Drug Master Files, and it makes it very clear that you're right, they are closed. But it also indicates the companies can make their own arrangements. So it isn't that they couldn't do that, it's just that I don't think it was done based on the evidence I have.

(Plunkett Depo 302:23-304:3). A party cannot raise an issue in a deposition, then complain that the expert answered the question. Dr. Plunkett's opinion that the finished dose manufacturers should have accessed the closed portions of the DMF flows from Dr. Plunkett's opinion that

finished dose manufacturers have a responsibility to ensure that the API they are purchasing and the finished dose they are selling do not contain unapproved harmful impurities. (Plunkett ¶ 55).

Dr. Plunkett elaborated on this a month later during her second day of deposition:

> Q. Are you aware of any guidance from FDA that requires an ANDA applicant to obtain access to the closed portion of a DMF?
>
> A. I think I answered that for you earlier. I said I don't recall – I don't – I don't think there's a specific language to the regulation to require it in the way you're stating it; however, they do require compliance of GMPs. And if the only way to ensure compliance in my view, for example, in this case, is to understand the details on whether or not the company making the API has – is complying with those GMPs having done the full risk assessment and all those things, I don't know how you do that without getting into some of the closed portion of the – of the Drug Master File. But I – That's – that's – I don't think that's what you're asking me, so I tried to answer it first. I don't believe there's specific language the way you are stating it, but that doesn't mean the finished-dose manufacturer doesn't have an obligation under the law, the regulations and also as set forth in the guidance to take steps to ensure that their drug that they're selling, their finished dose is, indeed, in compliance with GMP.
>
> Q. Well, maybe – let me try and break that down a little bit. You don't cite to any document in your report which identifies a requirement for a finished-dose manufacturer to obtain access to the closed portion of a DMF, do you?
>
> A. I don't state an – an opinion that way. No, I don't if that's what you're asking me. I don't have a statement that proactively states exactly what you did; however, I have opinions that are relevant to answering the question.
>
> Q. Understood. And I just want to be clear. You don't identify any document on your reliance list which requires a finished-dose manufacturer to obtain access to the closed portion of a DMF, do you?
>
> A. There's not, no. But again, it – what – what is the step there, as I discuss in my report, in the regulations for the finished-dose manufacturer that are applicable which would require them to take the steps they need to take to ensure that their product is being manufactured consistent with GMPs which, in my view, could include access to the closed portion. And in my experience working with companies, that's what companies have done.
>
> Q. So I just want to clarify. It is your opinion that any finished-dose manufacturer who does not obtain access to the closed portion of the DMF violation of CGMPs?

> A. No. I'm not implying that. That's a broader statement than I think I – I have stated. Do you want me to explain?
>
> Q. Maybe I can clarify. I understand it is your opinion in this case that the finished-dose manufacturers should have done that. Is it your opinion that any finished-dose manufacturer who does not also manufacture the API needs to obtain access to the closed portion of the DMF in order to comply with CGMP?
>
> A. I think that is not an opinion – opinion that I have formed at this time, no. However, I would couch that by saying that it's probably most important. I might have that – that opinion if you added the clause, in cases where the API manufacturer is using a process that is – that is different than the process that was part of the listing of the monograph for the referenced listed drug.

(Plunkett Depo 373:7-376:6, ECF 2285-6). Defendants had the opportunity to examine Dr. Plunkett about her opinions and potential testimony at her deposition. Defendants questioned Dr. Plunkett regarding her opinion that the finished dose manufacturers should have accessed the Drug Master File during her initial deposition. Defendants then called Dr. Plunkett back for a second day of deposition a month later and again questioned her on her opinion that the finished dose manufacturers should have accessed the closed portion of the Drug Master File. Thus, there are no grounds to exclude Dr. Plunkett's testimony in response to the Defendants' questions. Furthermore, as a regulatory expert, Dr. Plunkett is permitted to testify about what supply chain protocols a pharmaceutical company should implement in dealing with its suppliers. *See Yeazel v Baxter Healthcare Corp. (In re Heparin Prod. Liab. Litig.)*, 2011 WL 1059660, *4 (N.D. Ohio Mar. 21, 2011) ("may testify about appropriate supply chain protocols a pharmaceutical company should implement in dealing with its suppliers. He may tell jurors how a company should investigate its suppliers and their suppliers' sources, precautions needed to ensure the quality of raw ingredients throughout the supply chain, and what steps a company must take to avoid contamination and adulteration.").

CONCLUSION

For the foregoing reasons, Defendants' *Daubert* motion to exclude Dr. Plunkett's opinions should be denied.

Respectfully,

ON BEHALF OF PLAINTIFFS

By: /s/ C. Brett Vaughn

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Dated: April 11, 2023

CERTIFICATE OF SERVICE

I hereby certify that on this 11th day of April 2023, I caused a true and correct copy of the foregoing to be filed and served upon all counsel of record by operation of the Court's CM/ECF system. In addition, I certify that unredacted versions of the foregoing will be served contemporaneously upon liaison counsel for Defendants as well as the Court.

/s/ C. Brett Vaughn
C. Brett Vaughn